Amendment #2 to RFP NIH-NIAID-DAIDS-00-29

"SAFETY EVALUATION FOR ANTI-INFECTIVE THERAPIES"

Amendment to Solicitation:	NIH-NIAID-DAIDS-00-29
Amendment Number:	2
Amendment Issuance Date:	Thursday, December 2, 1999
Amendment Issued to:	ALL POTENTIAL OFFERORS
RFP Issue Date:	Wednesday, October 6, 1999
Proposal Due Date:	Thursday, December 30,1999, 4:00 P.M. EST(Unchanged)
Issued By:	Jacqueline C. Holden, NIAID, NIH Contract Management Branch 6700-B Rockledge Drive Room 2230, MSC 7612 Bethesda, Maryland 20892-7612
Point of Contact:	Ross Kelley, Contract Specialist

*The above numbered solicitation is amended as set forth below: The hour and date specified for receipt of offers is **NOT** extended. If by virtue of this amendment you desire to change an offer already submitted, such change may be made by telegram, letter or e-mail, provided each telegram, letter or e-mail makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.*

PURPOSE: To amend the cover letter, STATEMENT OF WORK ATTACHMENT A.2., ATTACHMENT F, and to provide a copy of the questions and answers concerning the RFP.

1. The Request for Proposal cover page is amended to add the following paragraph as paragraph two:

The government reserves the right to make award without discussions. Accordingly offerors are advised to submit their best offer and complete proposal information by the closing date of the RFP. The government reserves the right to hold negotiations if necessary.

STATEMENT OF WORK ATTACHMENT A.2., sections A.2.2, A,2,3., A.2.4, and A.2.6. are amended as follows:

2. Section A.2.2. PHARMACOKINETIC STUDIES, paragraph c. Clinical Pathology is amended as follows:

All dogs and monkeys will be fasted overnight and bled for clinical pathology once on Day -3 and again on Study Days 2, 6, 8, and 22. In no case will animals be bled from the intravenous treatment site. Clinical Pathology parameters will not be determined in rat PK studies.

3. Section A.2.3. ACUTE TOXICITY STUDIES IN RATS , paragraph c. Clinical Pathology, Clinical Chemistry is amended to add the following item:

- alanine aminotransferase (ALT) – IU/L

4. Section A.2.4. 28-DAY TOXICITY STUDIES IN RATS, first paragraph of subsection f., Micronucleus Evaluation is amended as follows:

Cells are flushed from one femur into fetal bovine serum. Cells are concentrated, and spread on ethanol-cleaned microscope slides, air-dried, and fixed for five minutes in absolute methanol. Three slides will be prepared and evaluated from every animal necropsied on day 28. Slides are stained with acridine orange and evaluated using epifluorescence microscopy at 630X or 1000X. Two hundred RBC are scored to determine the ratio of polychromatic erythrocytes (PCE) to RBC, and approximately 2000 PCEs are evaluated to determine the proportion with micronuclei.

5. Section A.2.6. 28-DAY TOXICITY STUDIES IN BEAGLE DOGS OR NON-HUMAN PRIMATES, paragraph a. Plasma Drug Level Determination is amended as follows:

Blood samples for determination of drug levels will be drawn from six animals (3 per sex) per dose group at 0 (immediately before dosing), 30, 60, 90, and 120 minutes, 3, 4, 6 and 8 hours after capsule administration on days 0, 6, 13, and 27. The same group of animals should be used for plasma drug studies on each specified day. The sample (approximately 2 ml) will be mixed with anticoagulant, centrifuged, and the plasma removed and frozen until analyzed. A blood sample will be drawn for plasma drug analysis prior to the sacrifice of moribund animals during the dosing period. Plasma drug levels will be determined using analytical procedures supplied by the Project Officer.

6. ATTACHMENT F., item 3.c.13. appendices is amended as follows:

*** HARDCOPY SUBMISSION OF Appendices: The following items are excluded from our electronic submission requirement and will not be subject to page limitations. Instead all Offerors may submit 10 paper copies of the information.*

- *A list of SOP titles; any other pertinent policy manuals; any letters of collaboration from other investigators; nonscannable figures or data.*

7. The following questions and answers are provided as part of this amendment:

1. A.2.2. Pharmacokinetic Studies: *What test parameters are required for Clinical Pathology? Verify that clinical pathology is only to be done on the dogs and monkeys and does not include the rat pk study.*

   Test parameters are up to the offeror to propose.

   Clinical pathology is to be done only in dog/monkey, but not rat, PK studies.

2. A.2.4. 28-Day Toxicity Studies in Rats: Clinical Pathology parameters include CBC, Chemistries (including electrolytes), and Prothrombin Times on Days –3, 7, 14, 21, 28, 35, 42, and prior to termination. This will require 2.5 mL blood be taken at each time point to include 0.5 mL for the CBC and retic, 1.0 mL for chemistries, and 0.9 mL for prothrombin time.

   A rat study showed 0.9 mL could be withdrawn weekly without causing any detectable changes in hematological parameters[1]. Generally, a maximum collection of 1% of body weight in a 2-week period is acceptable.[2] Assuming the minimum body weight of a female adult rat to be ~250 g this would be 2.5 mL of blood per 2 week period.

   Can we modify the timepoints and/or test parameters to reduce the amount of blood taken?

   You can modify timepoints and/or parameters as long as the modifications are justified, do not compromise the evaluation of the compound's safety, and are thus acceptable to the FDA.

   Pro Time evaluation should be deleted from the clin path panel.

3. A.2.4. 28-Toxicity Studies in Rats f. Micronucleus Evaluation. *Page out of order or necropsy on day 8 incorrect?*

   This is a misprint. It should read "necropsy on day 28", not day 8.

4. A. Protocol Reports 3. Statistical evaluation of differences between treatment and control groups. *ANOVA statistics or is mean, SD enough?*

   The RFP says "Statistical evaluation...." It's up to the offeror to propose an appropriate statistical evaluation.

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[1] Kurata M, et al: Effect of blood collection imitating toxicokinetic study on rat hematological parameters. J Toxicol Sci 22:455-459, 1997

[2] Reavill, The Veterimary Clinics of North America Exotic Animal practice Clinical Pathology and Sample Collection. W.B. Saunders Company Volume 2 Number 3 September 1999. Pg. 567

5. A.2.2 Pharmacokinetic Studies; 4. Measurements; d. Plasma Drug Level Determinations:

   Are the times for blood collection listed on Day 0 to be used following both intravenous and oral dosing? and Should animals be fasted overnight prior to both intravenous and oral dosing?

   No. Animals must be fasted prior to oral dosing and may be fasted prior to intravenous dosing.

6. *A.2.4. 28 Day Toxicity Studies in Rats, Measurements: c. Clinical Pathology:*

   Alanine transaminase (ALT) is not included in the clinical chemistry profile. ALT is a liver-specific enzyme in rats and is usually part of the chemistry profile. Should ALT be included in the Clinical Chemistry Profile?

   ALT should be included in the clinical chemistry profile.

7. *A.2.6. 28-Day Toxicity Studies in Dogs or Non-human Primates; for Measurements, e. Plasma Drug Level Determination:*

   Should the sentence stating "The same pair of animals . . . " actually read "The same groups of animals . . ."?

   Yes, it should read "groups".

8. *Determination of Genetic Toxicity:*

   For the micronucleus assay, are alternative scoring methods acceptable for use on the proposed program? MRI is aware of a kit available from Stratagene cloning systems in which MN are scored using a flow cytometric method. This is a rapid high throughput method.

   Yes, alternate scoring methods are acceptable.

9. My understanding of the Statement of Work is that item 1, parts a,b,c,d and e, requires the appropriate application of protocols provided in AttachmentA.2, and that item 2, parts a,b, and c, requires the development of protocols by the offeror. Is this understanding correct?

   Your understanding is correct

10. The Statement of Work, Item 1, part b, appears to require the application of protocols A.2.2, A.2.3, and A.2.4 to satisfy the pharmocokinetic, acute toxicity, and subchronic system toxicity determinations, but protocol A.2.4 states in it's objective that it is determining target organ toxicity which appears to also apply to item 2, part a. Am I applying the protocols provided in Attachment A.2 correctly?

    Yes

11. In the single administration study, it reads, "Only the fixed tissues from the control group, and highest dose group with minimal lethality will be embedded, blocked, sectioned and evaluated. The decision to examine tissues from the other dose groups will be made by the Study Director and Project Officer based on available information."

    In the multiple administration study, it reads, "Only the fixed tissues from the highest dose group with minimum lethality will be embedded and put into blocks. The decision to examine tissues from the other dose groups will be made by the Study Director and Project Officer based on available information." We assume that the control tissues from the multiple administration study should also be embedded and put into blocks. And we assume that all sectioned and evaluated as is written in the single administration study.

    Are these correct assumptions?

    Yes

Except as provided herein, all terms and conditions of the RFP document NIH-NIAID-DAIDS-00-29 remain unchanged and in full force and effect.

Offerors must acknowledge receipt of this Amendment #2 prior to the offer/proposal due date and time specified in the solicitation as amended, by one of the following methods:

1. By acknowledging receipt of the amendment on each copy of the offer submitted; or

2. By sending an electronic mail message to Ross Kelley, Contract Specialist, at rk17a@nih.gov which includes a reference to the solicitation and amendment number; or

3. By sending the Contracting Officer a separate letter or telegram which includes a reference to the solicitation and amendment number.

Failure to receive your acknowledgment of this amendment prior to the hour and date specified for proposal receipt may result in the rejection of your offer.